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Evaluation of real-life data in patients with severe eosinophilic asthma treated with mepolizumab

Mepolizumab ile tedavi edilen ağır eozinofilik astımlı hastalarda gerçek yaşam verilerinin değerlendirilmesi

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ABSTRACT

Aim: We aimed to evaluate the efficacy of mepolizumab on asthma exacerbations, blood eosinophils, oral steroid dependence, and asthma control.

Material and Method: This study is a clinical observational study created from real-life data obtained by retrospective analysis. Patients who were initiated subcutaneous mepolizumab at a dose of 100 mg every four weeks in our clinic and received treatment for at least 16 weeks were included in the study.

Result: Thirty-four patients with severe eosinophilic asthma were included in the study. We found that mepolizumab treatment resulted in a decrease in the number of asthma exacerbations, the need for maintenance oral corticosteroid, blood eosinophil counts, and improvement in lung functions and asthma control test scores in patients with severe eosinophilic asthma. At 6 months the rate of responders and super responders to mepolizumab treatment was 75% and 17.9%, respectively, and the overall response rate was 92.9% as a result. In the first year of treatment, the rate of super-responders increased to 58.3%, and the overall response rate was 91.7%. The rate of second-year responders and super-responders was 7.7% and 84.6%, respectively, and the overall response rate was 92.3%. At 3 years, the overall response rate had increased to 100%.

Conclusion: The results of our single-center study, in which we evaluated the results of mepolizumab treatment in patients with severe eosinophilic asthma, confirmed the clinical, hematological and functional findings published by previous studies in a real-life setting.

Keywords: Asthma control test, blood eosinophil counts, corticosteroid, interleukin – 5

ÖZ

Amaç: Mepolizumabın astım alevlenmeleri, kan eozinofilleri, oral steroid bağımlılığı ve astım kontrolü üzerindeki etkinliğini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu çalışma, retrospektif analiz ile elde edilen gerçek yaşam verilerinden oluşturulmuş klinik gözlemsel bir çalışmadır. Kliniğimizde dört haftada bir 100 mg deri altı mepolizumab başlanan ve en az 16 hafta tedavi gören hastalar çalışmaya alındı.

Bulgular: Ağır eozinofilik astımı olan 34 hasta çalışmaya dahil edildi. Ağır eozinofilik astımı olan hastalarda mepolizumab tedavisinin astım alevlenmelerinin sayısında, oral kortikosteroid idame ihtiyacında, kan eozinofil sayılarında ve akciğer fonksiyonlarında ve astım kontrol testi puanlarında iyileşme ile sonuçlandığını bulduk. 6 ayda mepolizumab tedavisine yanıt verenlerin ve süper yanıt verenlerin oranı sırasıyla %75 ve %17,9'du ve sonuç olarak genel yanıt oranı %92,9'du. Tedavinin ilk yılında, süper yanıt verenlerin oranı %58,3'e yükseldi ve genel yanıt oranı %91,7 oldu. İkinci yılda yanıt verenlerin ve süper yanıt verenlerin oranı sırasıyla %7,7 ve %84,6 ve genel yanıt oranı %92,3'tü. 3 yılda, genel yanıt oranı %100'e yükselmişti.

Sonuç: Ağır eozinofilik astımı olan hastalarda mepolizumab tedavisinin sonuçlarını değerlendirdiğimiz tek merkezli çalışmamızın sonuçları, gerçek yaşam ortamında önceki çalışmalarda yayınlanan klinik, hematolojik ve fonksiyonel bulguları doğruladı.

Anahtar Kelimeler: Astım kontrol testi, interlökin–5, kan eozinofil sayıları, kortikosteroid

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INTRODUCTION

Asthma is a heterogeneous disease characterized by chronic and variable airway inflammation, affecting more than 300 million people worldwide. Asthmatic patients differ not only in clinical features and disease severity, but also in underlying chronic airway inflammation, airway hyperresponsiveness, and airway remodeling. Among the different phenotypes and endotypes of asthma, eosinophilic inflammation is detected in more than 50% of patients, whether atopic or not (1). Severe eosinophilic asthma, which is associated with high numbers of eosinophils in both peripheral blood and airways, severe airflow limitation and recurrent asthma exacerbations, can often be controlled with the use of maintenance systemic corticosteroids (2,3).

Interleukin–5 (IL–5) is the main cytokine responsible for differentiation, maturation, activation and proliferation of eosinophils. Therefore, biological agents targeting IL–5 have been developed in severe eosinophilic asthma. Of these, mepolizumab is an IgG1/k class humanized monoclonal antibody that blocks IL – 5 by preventing its interaction with the α chain of the IL–5 receptor (4,5).

In randomized controlled studies, it has been shown that mepolizumab reduces asthma exacerbations and the dose of oral steroids used, has a significant lowering effect on blood eosinophils, and improves asthma control in severe eosinophilic asthmatics (6-9). The efficacy of mepolizumab in severe eosinophilic asthma has also been demonstrated in real-life studies and is now well established. However, these real-life studies are limited both in our country and worldwide. Therefore, we aimed to evaluate the efficacy of mepolizumab on asthma exacerbations, blood eosinophils, oral steroid dependence, and asthma control.

MATERIAL AND METHOD

The study was carried out with the permission of Health Sciences University Ankara Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date: 09.03.2021, Decision No: 2021-KAEK-15/2247). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Subject Characteristics and Study Design

This study is a clinical observational study created from real-life data obtained by retrospective analysis of patients in the Allergy and Immunology Clinic of Health Sciences University Ankara Keçiören Training and Research Hospital.

Patients who were initiated subcutaneous mepolizumab at a dose of 100 mg every four weeks in our clinic and received treatment for at least 16 weeks were included in the study. All patients had uncontrolled asthma (at least 2 attacks per year, requiring systemic corticosteroid use for at least 3 days) despite using high-dose inhaled corticosteroids (ICS) (>800 mcg/day budesonide or equivalent) and an inhaler long-acting β2-agonist, along with a third controller drug at least 1 year and/or had controlled or uncontrolled asthma under regular systemic steroids for at least 6 months and had a blood eosinophil count ≥300 cells/μL(for long-term regular systemic steroid users, ≥150 cells/μL under this treatment). All patients met the ATS/ERS criteria for uncontrolled severe asthma and defined conditions for mepolizumab according to the Turkish Social Security Institution (10).

Demographic data of the patients, their asthma diagnosis and follow-up times, information about whether they have been treated with omalizumab before, asthma control test (ACT) score at baseline and after mepolizumab injection, blood eosinophil count, FEV1 and FEV1/FVC values, oral corticosteroid (OCS) use Parameters including dose, asthma treatment step and number of attacks were obtained from the files of the patients. Asthma attack was defined as worsening of asthma symptoms requiring systemic corticosteroid use for at least 3 days. In the specified time periods (1st year, 2nd year and 3rd year); Patients who met one of the criteria for a ≥50% reduction in the number of asthma attacks compared to the previous year in those with a history of frequent exacerbations or a ≥50% reduction in daily OCS dose in continuous OCS users were defined as 'responder', while those who could discontinue OCS and had no exacerbations were defined as 'super-responders' (11).

Statistical Analysis

Predictive analytical software (PASW statistics 18, 2009) was used for the analysis. Descriptive statistics was expressed as numbers and percentages for categorical variables and as mean, standard deviation, median, percentile 25, percentile 75, minimum and maximum for numerical variables.

RESULTS

Baseline Patient Characteristics

Thirty-four patients with severe eosinophilic asthma were included in the study. The mean age of the study population was 49±12 years and 23 participants were female (67.6%). The mean body mass index (BMI) was 29±5 kg/m², and 12 patients (35.3%) were obese (BMI 30 Kg/m²). The median total IgE value of the patients before treatment was 414.98 (37-2500) kU/L. Atopy (26.5%) was detected in 9 patients according to skin test positivity and/or sIgE levels. The mean duration of asthma diagnosis of the patients was 14.24±8.05 years. Seventeen of the patients (50%) had previously received omalizumab treatment and were switched to mepolizumab due to partial response to omalizumab (**Table 1**).

Because the patients had a baseline ACT score of 16.62±4.72, these patients had poor symptom control. A mean of 2.38±1.84 asthma exacerbations occurred in patients in the year prior to the start of mepolizumab. The mean FEV1 values of the patients before mepolizumab treatment were 2375.86±733.22 (580-4340) mL. Of the 34 patients included in the study, 29 were using OCS and the mean OCS dose was 6.38±4.01 mg. Prior to mepolizumab treatment, the mean baseline eosinophil level was 885.47±728.06 /μL (min-max:150-3880).

Table 1. Baseline demographic and clinical characteristics

Variables	Baseline (N=34)
Age. (years)	49±12
Female. n (%)	23 (67.6)
BMI. (kg/m²)	29±5
Smoking story. n (%)	
Activesmoker	3 (8.8)
Never smoked	23 (67.6)
Ex-smoker	8 (23.5)
Asthma duration. (years)	14.24±8.05
Mean follow-up duration. (years)	6.65±3.96
Exacerbations (last 12 months)	2.38±1.84
Patients receiving maintenance OCS at baseline n (%)	29 (85.3)
Methylprednisolone equivalent OCS dose at baseline. (mg)	6.38±4.01
Baseline total IgE levels. (IU/mL)	414.98±556.84
History of treatment with omalizumab. n (%)	7 (50)
Atopy. n (%)	9 (26.5)
Perennial allergen sensitivity n (%)	9 (26.5)
Nasal polyposis. n (%)	20 (58.8)
Chronic eosinophilic pneumonia. n (%)	16 (47.1)

Follow-up Data with Mepolizumab

Six of the patients received mepolizumab for 16 weeks, 4 for 6 months, 11 for 1 year, 8 for 2 years, and 5 for 3 years. It was observed that the ACT score increased from 16.62±4.72 to 21±4.17 at the 4th week of mepolizumab treatment. The ACT score, which was 21.14±3.92 at week 24, increased to 22.5±3.46 at year 1, 24.23±1.17 at year 2, and 24±1.41 at year 3. When we look at the effect of mepolizumab on blood eosinophil values (respectively: absolute value, percent) compared to baseline values (885.47±728.06/μL, 8.69±7.36%), a decrease was achieved at 4 weeks (147.29±141.84/μL, 1.6±1.73%). This decrease in blood eosinophil values continued at other time points; 116.96±120.96/μL, 1.49±1.3% at week 24, 131.76±97.87μL, 1.54±1.14% at 1 year, 97.5±57.23/μL, 1.13±0.66% at Year 2 and 100±58.31/μL, 1.08%±0.63% at year 3. The mean FEV1 values measured to evaluate the improvement in lung functions were 2375.86±733.22 mL at baseline, 2675±658.04 mL at week 4, 2620±535.82 mL at week 24, 2777.78±645,38 mL at year 1, 2820±296.98 mL at year 2. While the patients receiving daily OCS were 29 at baseline, it decreased to 19 at 24 weeks, 7 at 1 year, and 1 at 2 years. In the 3rd year, there were no patients who received daily OCS. While the median daily dose of OCS was 6.38±4.01 mg in the premepolizumab period, it decreased to 2.24±1.81 mg at week 24. The mean number of asthma exacerbations in the year before mepolizumab treatment was 2.38±1.84, compared to 0.79±1.14 in the first year, 0.23±0.6 in the second year, and 0.4±0.89 in the third year after treatment (**Table 2**).

When maintenance asthma treatments were evaluated, 47.1% of the patients were receiving high-dose ICS+ Long-Acting Beta-Agonists (LABA) and 52.9% were receiving medium-dose ICS+LABA at baseline. While the rate of those using high-dose ICS+LABA in the first year with mepolizumab treatment decreased to 33.3%, the rate of those using medium-dose ICS+LABA increased to 62.5%. The remaining patients were receiving low-dose ICS+LABA therapy. In the second year after mepolizumab treatment, the proportion of those using high-dose ICS+LABA decreased to 7.7%, while the proportion of those receiving medium-dose ICS+LABA and low-dose ICS+LABA treatment increased to 76.9% and 15.4%, respectively.

At 6 months the rate of responders and super responders to mepolizumab treatment was 75% and 17.9%, respectively, and the overall response rate was 92.9% as a result. In the first year of treatment, the rate of super-responders increased to 58.3%, and the overall response rate was 91.7%. The rate of second-year responders and super-responders was 7.7% and 84.6%, respectively, and the overall response rate was 92.3%. At 3 years, the overall response rate had increased to 100%.

Table 2. Comparison of clinical. laboratory and functional parameters at baseline 24th weeks and 1st. 2nd. 3rd years

Variables	Pre-mepolizumab n: 4	Mepolizumab 24th week, n: 28	Mepolizumab 1st year, n: 24	Mepolizumab 2nd year, n: 13	Mepolizumab 3rd year, n: 5
ACT score	16.62±4.72	21.14±3.92	22.5±3.46	24.23±1.17	24±1.41
Blood eosinophil count (cell/mm³)(%)	885.47±728.06 8.69±7.36	116.96±120.96 1.49±1.3	131.76±97.87 1.54±1.14	97.5±57.23 1.13±0.66	100±58.31 1.08±0.63
FEV1, (mL)	2375.86±733.22	2620±535.82	2777.78±645.38	2820±296.98	-
OCS dosage. (mg/day)	6.38±4.01	2.24±1.81	2.9±2.44	8	0
Attack number	2.38±1.84	0.25±0.5	0.79±1.14	0.23±0.6	0.4±0.89

Abbreviations: ACT: Asthma control test, FEV: Forced expiratory volume, OCS: Oral corticosteroid

At the sixth month of mepolizumab treatment, the duration of asthma diagnosis was shorter in unresponsive patients compared to responders and superresponsive patients (15.24±8.69, 11.6±6.39, and 8±0 years, respectively). Blood eosinophil counts were also lower in responding and superresponsive patients compared to non-responders (822.1±509.58, 684±493.74, and 2261±2289.61/μL, respectively). The number of patients receiving maintenance OCS treatment was higher in responding and superresponsive patients than in non-responders (90.5%, 80% and 50%, respectively). Baseline total IgE levels were higher in responding and superresponsive patients compared to non-responders (465.13±673.3 IU/mL, 461.4±439.38 IU/mL, and 117 IU/mL, respectively). The presence of nasal polyps with asthma was higher in responding and superresponsive patients than in non-responders (66.7%, 40%, and 0%, respectively).

Blood eosinophil counts were higher in responding and superresponsive patients at 1 year than in nonresponders (1474±1086.45/μL, 800.29±439.36/μL, and 425±35.36/μL, respectively). Baseline total IgE levels were higher in responding and superresponsive patients compared to non-responders (955.02±1130.81 IU/mL, 395.12±357.11 IU/mL, and 08.25±99.35IU/mL, respectively). In the second year, blood eosinophil counts were higher in responding and superresponsive patients than in non-responders (1330 /μL, 942.36±533.49/μL and 740/μL, respectively).

Safety and Tolerability of Mepolizumab

Treatment with mepolizumab was well tolerated and no side effects were reported in our patients.

DISCUSSION

In this study, we found that mepolizumab treatment resulted in a decrease in the number of asthma exacerbations, the need for maintenance OCS, blood eosinophil counts, and improvement in lung functions and ACT scores in patients with severe eosinophilic asthma.

The number of eosinophils is increased in the blood, lung tissue and airway mucosa of patients with severe eosinophilic asthma. Blood eosinophils are associated with sputum eosinophils, and high blood eosinophil counts indicate good specificity for airway eosinophilia. IL-5 is a pro-eosinophilic cytokine responsible for differentiation, maturation, activation and proliferation of eosinophils (12). Mepolizumab, which acts by blocking IL-5, has been shown in randomized controlled trials known as DREAM, MENSA and SIRIUS to provide asthma control, reduce the dose of oral steroids and have a significant lowering effect on blood eosinophils in severe eosinophilic asthmatics (6-8). After mepolizumab's approval for use, studies on its real-life effectiveness were conducted. In our study, we showed that mepolizumab reduced the number of asthma exacerbations, improved ACT scores, decreased blood eosinophil counts, decreased need for maintenance OCS, and improved lung function, similar to the aforementioned randomized controlled trials and real-life studies (1,2,4,11-18).

Regarding asthma symptom control, a rapid improvement in ACT scores was observed in our patients starting from the fourth week. Many previous real-life studies have also used ACT to assess asthma control and mepolizumab has been shown to improve asthma control (15,18-20). In our study, a rapid and striking decrease was observed in blood eosinophil counts along with rapid improvement in asthma control. This data of our study was compatible with the literature (4,11,21,22).

In severe eosinophilic asthma, blood eosinophils are reliable biomarkers both for compliance with mepolizumab therapy and for predicting response to therapy (12,23). In our study, a decrease in blood eosinophil counts was observed from the first 4 weeks of treatment. The decrease in blood eosinophil counts continued throughout the duration of the treatment.

One of the main goals in patients with severe eosinophilic asthma is to reduce the steroid dose. In our study, with the gradual decrease in the maintenance OCS dose used in our patients together with mepolizumab treatment, maintenance OCS intake was discontinued in many patients. In a prospective observational study of 61 patients in Israel, the daily dose of OCS was reduced or discontinued in 68% of patients on continuous OCS before mepolizumab (24). In a retrospective real-life study evaluating 138 patients from 11 centers in Italy, it was observed that 66% of OCS-dependent patients stopped taking OCS at the end of the first year, and the dose of OCS decreased from 10.1±9.4 mg/day to 2 mg/day (14). Mepolizumab treatment also reduced the number of asthma exacerbations in patients. Our data were consistent with studies in the literature evaluating the use of mepolizumab in severe eosinophilic asthma (6,7).

In our study, we did not find any finding that enables us to predict which patients will respond or super-responsive to mepolizumab. However, in randomized controlled studies, it was determined that the higher the eosinophil count before treatment, the better the response to treatment (7,25). In a multicenter Australian study of 309 patients, patients identified as responders had higher blood eosinophil levels and lower maintenance OCS use. The same study found that super-responders were less symptomatic at baseline and required less OCS therapy for exacerbations in the previous year (17).

There are some limitations of our study. The first of these was that our study was a retrospective and single-center study. The second was that the statistical results were limited due to the small number of patients included in the study and the unequal number of patients at the specified time points.

CONCLUSION

The results of our single-center study, in which we evaluated the results of mepolizumab treatment in patients with severe eosinophilic asthma, confirmed the clinical, hematological and functional findings published by previous studies in a real-life setting.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University Ankara Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date: 09.03.2021, Decision No: 2021-KAEK-15/2247).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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